REMARKS

Claims 11, 16-20, and 22-26 are pending in the instant application. Claims 16 and 22 have been cancelled, without prejudice to Applicants' right to pursue the subject matter of the claims in this or related applications. Claim 11 has been amended to clarify the subject matter of the present invention and to round out the scope of protection to which Applicants are entitled; i.e., the claim amendment was not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103, or 112. Reconsideration and withdrawal of all rejections of the application, and allowance of the claims, especially in view of the amendments and remarks made herein and the documents herewith, are respectfully requested.

The previous response, filed on November 27, 2002, reviewed the contrast between the present invention and the state of the art at the time the instant application was filed. The potential for peripheral mechanisms to play a significant role in the mediation of antinociceptive responses was unknown prior to the teaching of the present invention. Opioid analgesia was thought to be mediated through the central nervous system (i.e., systemically) rather than through peripheral opioid receptors. Those skilled in the art did not appreciate the significance of peripheral opioid receptor stimulation, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. Methods of the present invention comprising topical administration of opioid analgesics and local anesthetics unexpectedly produce synergistic pain relief in the periphery, even in small, non-systemic dosages ranges.

In response, the Office Action of February 26, 2003 asserts that claimed invention is obvious under 35 U.S.C. § 103(a) in view of the combination of Stein (U.S. Patent No. 5,948,389) and Saito et al. Stein involves administration of topical compositions comprising opioid analgesics and/or local anesthetics that must be contained in hyperosmolar solutions. Saito reports that systemic administration of morphine and lidocaine—at dosages outside of the claimed ranges—produces a synergistic antinociceptive response in rats. The Office Action correctly states that Stein and Saito, taken together, do not teach the employment of a single composition comprising both morphine and lidocaine. However, the Office Action then states that administration of a topical composition comprising both drugs would have been obvious to one of ordinary skill in the art on the basis of the cited documents. The cited documents do not teach or suggest the claimed methods because, inter alia:

- Concentrations of morphine and/or lidocaine that are said to be synergistic do not fall within the scope of the claims and therefore, have no bearing on the efficacy of the claimed compositions.

- There is no teaching or suggestion of a topical composition acting solely in the periphery, much less one having synergistic effects.

In addition to the challenges made to the cited documents herein, the position of the Office is now rebutted by further evidence of non-obviousness. The data contained in the instant application was published in the Journal of Pharmacology and Experimental Therapeutics ("the Journal"). *See* Kolesnikov et al., (2000) J. Pharm. Exp. Therapeutics, Vol. 295 (2), which is submitted concurrently in the accompanying Supplemental Information Disclosure Statement as reference AQ. Submitted herewith is the declaration of Sandra C. Roerig, Ph.D. under 37 C.F.R. § 1.132, editor for the Journal, forwarding the statements of reviewers for the Journal who analyzed the data of the instant application on May 19, 2000 and found the results to be unexpected. It is respectfully submitted that the Office Action employs an improper hindsight combination of cited documents and an artificial view of the art. Moreover, it is respectfully asserted that the combination of documents and views in the Office Action are clearly and convincingly overcome by actual statements by those skilled in the art attesting to the surprising nature of the claimed methods.

Also submitted herewith is a copy of Exhibit A to accompany the Declaration filed on December 2, 2002 under 37 C.F.R. § 1.131.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH ARE OVERCOME

Applicants respectfully traverse the rejections of claims 11, 16-20, and 22-26 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleges that the particular limitation in claim 11, "to potentiate a synergistic antinociceptive response at peripheral sites" lacks support from the specification or claims as originally filed.

In response, Applicants respectfully direct the Examiner to page 19, lines 6-8, 12-14, and 20-22 of the specification as originally filed. The specification clearly recites on page 19, lines 6-8 that "[s]ynergistic potentiation of analgesia through topical administration of a local anesthetic/opioid combination offers a new approach to peripheral pain management". The specification also recites on page 19, lines 12-14 that "[i]t has now been found that topical administration of a composition comprising certain relative amounts of opioids and local anesthetics results in the synergistic potentiation of peripheral antinociceptive responses". Furthermore, the specification utilizes the terminology "potentiated antinociceptive response" as "a pain-reducing response elicited through the synergistic effect of at least one opioid and at least one local anesthetic, in which the combined effect is greater than the sum of the effect produced by either agent alone". Thus, Applicants respectfully submit that the particular limitation in claim 11, "to potentiate a synergistic antinociceptive response at peripheral sites" is unambiguously supported in the specification as originally filed and respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

THE REJECTIONS UNDER 35 U.S.C. § 103 ARE OVERCOME

Applicants respectfully traverse the rejections of claims 11, 16-20, and 22-26 under 35 U.S.C. § 103, in view of Stein and Saito. The cited documents, taken alone or together, fail to teach or suggest methods of administering the topical compositions of the present invention.

The claimed methods relate to the administration of topical compositions having a concentration of morphine from about 0.01% to about 25% and the concentration of lidocaine from about 0.01% to about 25%. The exemplary concentrations of morphine and/or lidocaine in the cited documents do not fall within the scope of the claims and therefore, have no bearing on

the efficacy of, and fail to teach or suggest, the claimed methods. Moreover, the cited documents fail to teach or suggest a topical composition acting solely in the periphery, much less one having synergistic effects.

U.S. Patent No. 5,948,389 ("Stein")

The Stein patent is directed to topical administration of hyperosmolar solutions of opioids or anesthetics (or mixtures) such that the drugs first pass into non-inflamed tissue in order to reach inflamed tissue. Stein does not teach or suggest administration of topical compositions having only local effects in the periphery, or the benefit thereof. This marks a clear distinction between Stein and the present invention.

Importantly, Stein does not teach or suggest that there is a synergistic effect between opioid analgesics and local anesthetics at peripheral sites, which is an unexpected result of the present invention. In fact, Stein does not teach that use of two agents in combination would be any better than the use of a single agent alone, much less synergistic.

Stein states only that a range between 0.5% and 95% (w/v) of drug in solution of osmolality between 300-700 mOsm/L can be used. No exemplification of lidocaine or morphine is provided. Therefore, the skilled artisan would have no reasonable expectation that a topical combination of lidocaine and morphine in the claimed dosage ranges would have a synergistic effect. Saito also fails to teach synergy in the claimed dosage ranges; and, as a result, the combination of the documents employed in the Office Action fails to cure the deficiencies of both Stein and Saito to teach or suggest the instant invention.

Applicant's previous response, filed on November 27, 2002, presented several studies which demonstrated that the topical administration of morphine was discouraged in a clinical setting. The Office Action relies upon Stein to allegedly define the state of the art at the time the instant application was filed. It is compelling that that Stein provides no exemplification whatsoever for the use of topical morphine. As such, Stein does not carry sufficient weight to reverse the well established and widely held view in the art that topical morphine is not an effective pain reliever.

The response filed on November 27, 2002 presented information relating to hundreds of patients who failed to receive any benefit from morphine treatment at peripheral sites. *See*

Moore et al.[1] (describing two consecutive studies on twenty patients treated with a topical morphine gel); Raja et al.[2] (describing a randomized, double-blinded study comparing the analgesic efficacy of bupivacaine and morphine administered intraarticularly in 47 patients having undergone arthroscopic knee surgery); Rosenstock et al.[3] (describing a double-blind, randomized, placebo-controlled study to evaluate the possible immediate and long-term analgesic effect of morphine injected incisionally in patients undergoing minor abdominal surgery); Picard et al.[4] (reviewing 26 randomized controlled trials studied 925 patients, of which 485 received peripherally-acting opioids, including morphine, fentanyl, alfentanil, buprenorphine and butorphanol); Yarussi et al.[5] (describing a study to evaluate the post-operative analgesic effects of incisionally-administered morphine in 45 patients undergoing lumpectomies and axillary node dissections in the treatment of breast cancer).

Therefore, contrary to the position of the Office, Stein does not outweigh prior teachings in the art that discourage the use of topical morphine in among a great number of patients.

Saito et al.

Saito teaches the intrathecal (i.e. systemic), but not topical, administration of an opioid in combination with an anesthetic, whereby such co-administration leads to a synergistic analgesic effect. The teaching of a systemic administration of an opioid is contrary to the instant invention. At best, Saito continues to emphasize the views of those skilled in the art—that analgesic actions are mediated through the central nervous system. Nowhere in Saito is it suggested that combinations of analgesics and local anesthetics can synergistically stimulate peripheral sites.

When morphine and lidocaine were administered together in Saito, the following concentrations (in percent w/v) were used: 0.12% morphine (0.3 μg/kg/h in 250 μl volume) and 80% lidocaine (200 μg/kg/h in 250 μl volume); 1.2% morphine (3 μg/kg/h in 250 μl) and 12%

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[1] Moore UJ, Seymour RA, Gilroy J, Rawlins MD. (1994) "The Efficacy of Locally Applied Morphine In Post-Operative Pain After Bilateral Third Molar Surgery," Br. J. Clin. Pharmacol. 37:227-30.
[2] Raja SN, Dickstein RE, Johnson CA. (1992) "Comparison of Postoperative Analgesic Effects of Intraarticular Bupivacaine and Morphine Following Arthroscopic Knee Surgery," Anesthesiology 77:1143-7.
[3] Rosenstock C, Andersen G, Antonsen K, Rasmussen H, Lund C. (1996) "Analgesic Effect of Incisional Morphine Following Inguinal Herniotomy Under Spinal Anesthesia," Reg. Anesth. 21:93-8.
[4] Picard PR, Tramer MR, McQuay HJ, Moore RA. (1997) "Analgesic Effect of Peripheral Opioids (all except intra-articular): A Qualitative Systematic Review of Randomised Controlled Trials" Pain 72:309-18.

lidocaine (30 μg/kg/h). **Only the combination of 1.2% morphine and 12% lidocaine falls within the scope of the claims. The results reported by Saito in this range were not shown to be greater than additive, i.e., not synergistic.**

Only the Saito abstract was cited against the instant application.[6] Upon examination of the article in full text, it is apparent that the authors do not conclude that the combination of 1.2% morphine and 12% lidocaine produces a synergistic response. The Examiner's attention is respectfully directed to Figure 4 of the Saito reference, depicting the time course effects of 1.2% morphine (3 μg/kg/h in 250 μl) and 12% lidocaine (30 μg/kg/h), administered by intrathecal infusion. No further analysis of this combined dosage was performed and therefore, no synergy was reported.

Measurement of synergy in Saito is performed by isobolographic analysis (Figure 5), using three dose-effect curves: one for morphine, one for lidocaine and one for the combination at a fixed dosage having a morphine:lidocaine ratio of 1:200. *See* Saito, page 1457 (stating "[t]o perform isobolographic analysis, the dose ratio of the combination was fixed at a morphine:lidocaine ratio of 1:200") and page 1458 under "*Isobolograpgic Analysis.*" Combination doses outside of the claimed dosage ranges were used in the isobolographic analysis (i.e., between 30 μg/kg/h and 600 μg/kg/h lidocaine). **Therefore, the isobolographic analysis in Saito does not show that the combination of 1.2% morphine (3 μg/kg/h in 250 μl) and 12% lidocaine (30 μg/kg/h) produces a synergistic effect.**

Accordingly, the authors state only that the higher combination of 0.12% morphine and 80% lidocaine "may indicate synergistic antinociceptive effects." *See* Saito, page 1460. Moreover, the authors do not find these results to be relevant to any other dosage range or mode of administration, stating "[t]he magnitude of the synergistic effects depends on the concentration of infused drugs when the infusion is constant." *Id.* Therefore, Saito does not teach or suggest synergy in the claimed dosage ranges.

Finally, nowhere in Saito is it demonstrated or suggested that the observed antinociceptive effects occur at peripheral sites. The authors carefully define the limits of their

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[5] Yarussi A et al. (1999) "Evaluation of Peripheral Morphine Analgesia for Lumpectomy and Axillary Node Dissection: A Randomized, Double-blind, Placebo-controlled Study," Reg. Anesth. Pain. Med. 24:142-5.

[6] It is respectfully noted that the Board of Patent Appeals and Interferences has admonished the Examining Corps to not cite only abstracts of documents in making rejections. *See Ex Parte Jones,* 62 U.S.P.Q. 1206 (Pat. & Tr. Office Bd. App. 2001).

study, stating that morphine and lidocaine were selected to "evaluate the antinociceptive interaction of opioid and local anesthetics at the spinal level..." *See* Saito, page 1461 (emphasis added). At the time the instant application was filed, a showing of antinociception by a composition acting in the central nervous system had no bearing on its potential for action in the periphery, and nothing in Saito suggests otherwise. Thus, Saito, like Stein, does not teach or suggest topical compositions having only local effects in the periphery, or the benefit thereof.

Given the lack of exemplification in Stein, the lack of relevant synergistic efficacy in Saito, and the failure of both references to disclose or suggest compositions having a localized topical effect, it is respectfully submitted that the cited documents fail to teach or suggest the claimed methods. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

Declaration of Sandra Roerig, Ph.D. Under 37 C.F.R. § 1.132

Submitted herewith is the declaration of Sandra C. Roerig, Ph.D. under 37 C.F.R. § 1.132, as editor for the Journal of Pharmacology and Experimental Therapeutics ("the Journal"). The data contained in the instant application was published in the Journal. Dr. Roerig attests to the May 19, 2000 statements of reviewers for the Journal who in the ordinary course of business analyzed the data of the instant application (e.g., depicting the synergistic effect of topical compositions of morphine and lidocaine in mice) and found the results to be unexpected. Specifically, the reviewers found that the synergy produced by the claimed methods was "profound" and "quite marked." One of the reviewers further stated that studies of this kind had "never been performed previously." It was their view, as communicated by Dr. Roerig, that the results were unexpected and therefore, non-obvious.

The statements of the reviewers are in contrast to the position of the Office, which is stated as follows on pages 3-4 of the Office Action:

> A person of ordinary skill in the art would have been motivated to make and use a topical composition, which comprises morphine and lidocaine because lidocaine and morphine in combination are known to provide synergistic antinociceptive effects, and because they are known to be employed in combination.

Prior to the teaching of the present application, morphine and lidocaine were not known to synergistically potentiate the antinociceptive effects of each other in the periphery. The extent

to which they interact in the periphery, as first shown by the Applicants, was stated to be "profound" and "quite marked" by those skilled in the art. In this regard, the claimed nethods exhibit unexpected and surprising effects.

The Office Action further states on page 4:

> [I]ntraconversion of dosage forms of optimization of the effective amounts of each ingredient to provide a known synergistic effect are within the skill of the artisan and therefore obvious. Regarding the particular limitation about the sites of synergistic antinociceptive response, note since the references teach synergistic antinociceptive effects generally, and would encompass any synergistic antinociceptive response.

Stein does not teach topical compositions having only local effects in the periphery, nor does Stein teach topical application of morphine or lidocaine in the claimed dosage ranges with any reasonable expectation of success. Any reasonable expectation of success could not come from the teaching of Stein and Saito, and the general knowledge in the art, but rather could only come from the teaching of the present invention. Optimization of synergistic amounts for topical application in the periphery was not a matter of routine variation based on existing art and in no way expected, as stated by the Journal reviewers. This position is further supported by Saito, which also emphasizes the importance of sufficient drug concentration in achieving synergy. *See* Saito, page 1460.

It is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Only through the exercise of impermissible hindsight have the cited references (i.e., Saito and Stein) been selected and relied upon by the Office. Systemic combinations of opioids and analgesics are non-analogous art, having no bearing on the function of topical compositions providing only localized effects in the periphery. As such, the skilled artisan working to develop a localized peripheral pain reliever and methods of its use is not motivated by literature describing systemic responses.

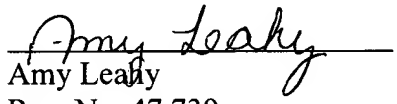
The view of the art allegedly conveyed by the cited references is unequivocally overcome by actual statements made by those skilled in the art attesting to the surprising nature of the claimed compositions. Withdraw of all rejections under 35 U.S.C.§ 103(a) is requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

In view of the declaration and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The Commissioner is hereby authorized to charge any additionally required fee occasioned by this paper, or credit any overpayment in this case, to Deposit Account No. 50-0320.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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FULL TEXT OF CASES (USPQ2D)
Cases Publishing the Week of Apr 15, 2002

(Unpublished) Ex parte Jones, 62 USPQ2d 1206 (BdPatApp&Int 2001)

62 USPQ2D 1206
Ex parte Jones
U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences

Appeal No. 2001-1839
Decided November 28, 2001

Unpublished Opinion

(Non-precedential)

Headnotes

PATENTS

[1] Patentability/Validity — Obviousness — Combining references (§115.0905)

"Motivation" to combine teachings of prior art is not always required to support obviousness rejection under 35 U.S.C. §103, since legally sufficient rationale for finding of obviousness may be supported by reason or suggestion in prior art, as well as motivation, to combine teachings.

[2] Practice and procedure in Patent and Trademark Office — Board of Patent Appeals and Interferences — Rules and rules

practice (§110.1105)

Patentability/Validity — Obviousness — Relevant prior art — In general (§115.0903.01)

Patent examiner's citation of abstract in support of rejection without citation and reliance on underlying scientific article is generally inappropriate if both abstract and underlying document are prior art, and proper examination therefore should be based on underlying documents and translations, if necessary, since abstracts often are not written by author of underlying document, and may be erroneous; in present case, in which neither examiner nor applicant relies on underlying articles, Board of Patent Appeals and Interferences, in exercise of its discretion, will not obtain translations of underlying journal articles in order to evaluate merits of translations in first instance, since it is examiner's responsibility to obtain translations, and since review of translations by examiner and applicant may supply additional evidence as to whether there is legally sufficient reason, suggestion, teaching, or motivation to combine teachings of cited articles, and thus may eliminate need for appeal.

Case History and Disposition

Patent application of Jones, serial no. 08/947,428.1 Applicant appeals from examiner's rejection of claims 38 and 39 in application. Vacated and remanded.

[Editor's Note: The Board of Patent Appeals and Interferences has indicated that this opinion is not binding precedent of the board.]

Judge:

Before Winters and William F. Smith, administrative patent judges, and McKelvey, senior administrative patent judge.

Footnotes

1 Application for patent filed 8 October 1997.

Opinion Text

Opinion By:

McKelvey, S.J.

Decision on appeal under 35 U.S.C. § 134

[Unpublished] The appeal is from a decision of a primary examiner rejecting claims 38-39. We vacate and remand for action not inconsistent with views expressed herein.

A. Findings of fact

[Unpublished] The record supports the following findings by at least a preponderance of

the evidence.2

[Unpublished] 1. The claimed invention relates to a method of making organic chemicals.

[Unpublished] 2. The examiner has rejected claims 38-39 as being unpatentable under 35 U.S.C. §103(a) over

[Unpublished] a) Horner,
[Unpublished] b) Suri,
[Unpublished] c) Endel'man,
[Unpublished] d) Manthey and
[Unpublished] e) Ota.

[Unpublished] 3. Horner is a 25-page technical journal article written in German.

[Unpublished] 4. The examiner has placed in the record a short English-language abstract of Horner.

[Unpublished] 5. The record does not contain an English-language translation of Horner.

[Unpublished] 6. Suri is a 2-page technical journal article written in English.

[Unpublished] 7. Endel'man is a 4-page technical journal article written in Russian.

[Unpublished] 8. The examiner has placed in the record a short English-language abstract of Endel'man.

[Unpublished] 9. The record does not contain an English-language translation of Endel'man.

[Unpublished] 10. Manthey is a 5-page technical journal article written in English.

[Unpublished] 11. Ota appears to be a 5-page technical journal article written in Japanese.

[Unpublished] 12. The examiner has placed in the record a short English-language abstract of Ota.

[Unpublished] 13. The record does not contain an English-language translation of Ota.

[Unpublished] 14. The examiner does not maintain that any one of the five prior art references fully describes the claimed invention. Hence, a rejection based on 35 U.S.C. §103(a).

[Unpublished] 15. According to the examiner, "the skilled artisan looking for an alternative route for the preparation" of the product produced by the claimed method "was deemed to be aware of all the various methods of the preparation" of the product (Examiner's Answer, page 4).

[Unpublished] 16. Further according to the examiner, "one of ordinary skill in the art would be motivated [sic—would have been motivated] to prepare *** [the compound made by applicant's claimed method] by coupling Suri's *** acid and Endel'man's *** acid as taught by Manthey followed by *** [further treatment] to yield *** [a compound] as taught by Horner and subsequent reduction as taught by Ota to arrive at the *** [claimed process]"(Examiner's Answer, pages 4-5).

[Unpublished] 17. According to applicant, the requisite "motivation" is not present in the prior art because "[t]hroughout the prosecution the examiner has failed to point out any teaching or suggestion in the prior art that would motivate the skilled artisan" to use the claimed process invention (Appeal Brief, page 4).

B. Discussion

1. Rationale in support of obviousness

[Unpublished]

[1] The applicant and the examiner have apparently assumed that there always must be "motivation" to combine teachings of the prior art to support a rejection based on §103(a). The assumption is not correct. The word "motivation" or a word similar to "motivation"does not appear in 35 U.S.C. § 103(a). While a finding of "motivation"supported by substantial evidence probably will support combining teachings of different prior art references to establish a *prima facie* obviousness case, it is not always necessary. For example, where a claimed apparatus requiring Phillips head screws differs from a prior art apparatus describing the use of flathead screws, it might be hard to find motivation to substitute flathead screws with Phillips head screws to arrive at the claimed invention. However, the prior art would make it more than clear that Phillips head screws and flathead screws are viable alternatives serving the same purpose. Hence, the prior art would "suggest"substitution of flathead screws for Phillips head screws albeit the prior art might not "motivate" use of Phillips head screws in place of flathead screws.

[Unpublished] What must be established to sustain an obviousness rejection is a legally sufficient rationale as to why the claimed subject matter, as a whole, would have been obvious notwithstanding a difference between claimed subject matter and a reference which is prior art under 35 U.S.C. § 102. Once a difference is found to exist, then the examiner must articulate a legally sufficient rationale in support of a §103(a) rejection. The legally sufficient rationale may be supported by a reason, suggestion, teaching *or* motivation in the prior art which would have rendered obvious the claimed subject within the meaning of § 103(a). *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637(Fed. Cir. 1998) (there must be some *teaching, suggestion* or *motivation* in the prior art to make the specific combination that was made by the applicant); *In re Gartside*, 203 F.3d 1305, 1319, 53 USPQ2d 1769, 1778(Fed. Cir. 2000) (the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a *teaching* or *motivation* to combine prior art references); *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*

, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629(Fed. Cir. 1996) ("there must be a *reason, suggestion*, or *motivation* *** to combine [the teachings of] *** references ***"); *Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1356, 51 USPQ2d 1415, 1420-21 (Fed. Cir. 1999) (there is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention; the relevant inquiry is whether there is a *reason, suggestion*, or *motivation*in the prior art that would lead one of ordinary skill in the art to combine the teachings of the references).

[Unpublished] Moreover, when an examiner maintains that there is an explicit or implicit teaching or suggestion in the prior art, the examiner should indicate where (page and line or figure) such a teaching or suggestion appears in the prior art. *In re Rijckaert*, 9 F.3d 1531, 1533, 28 USPQ2d 1955, 1957(Fed. Cir. 1993), citing *In re Yates*, 663 F.2d

1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981).

[Unpublished] One difficulty with the rationale in support of the examiner's rejection in this case, and for that matter the applicant's challenge to the rejection, is that it appears to be based solely on a motivation rationale without taking into account whether there otherwise is a legally sufficient *reason*, *showing*, *suggestion*or *teaching* which might also suffice to support the examiner's rejection. Moreover, a suggestion, teaching or motivation to combine teachings of the prior art may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617(Fed. Cir. 1999). *See also In re Gartside, supra* at 1319, 53 USPQ2d at 1778 (the suggestions may come from, *inter alia*, the teachings of the references themselves and, in some cases, from the nature of the problem to be solved).

[Unpublished] If the examiner determines that it is appropriate to enter a further rejection, the examiner may wish to consider a rationale based on a suggestion, teaching or other reason in place of a rationale based exclusively on motivation.

[Unpublished] We will also note that the examiner's theory of rejection, at least in part, seems to rely on the proposition that *if* a person of ordinary skill in the art is looking for an alternative method for the preparation of a compound, then that person would be aware of all analogous art (*see* Finding 15). If the examiner continues to rely on that theory, then the examiner would be under a burden to establish why a person of ordinary skill in the art would be looking for an alternative method, particularly where a method is known for making a particular compound.

2. *Use of abstracts in place of underlying articles*

[Unpublished] The principal difficulty with the prosecution of the application on appeal is the examiner's attempt to establish "motivation" by reliance on three English-language abstracts of journal articles written in foreign languages. The examiner does not maintain that only Suri and Manthey, both in English, support the rejection. The use of abstracts, when the underlying document is prior art, gives us considerable pause.

[Unpublished] The Board of Patent Appeals and Interferences continues to have recurring problems in resolving *ex parte* appeals which come before it. One continuing recurring problem is the citation and reliance by examiners on abstracts, without citation and reliance on the underlying scientific document.

[Unpublished]

[2] In this appeal, the examiner relied upon abstracts of three technical journal articles without referring to translations of the underlying documents. Citation of an abstract without citation and reliance on the underlying scientific document itself is generally inappropriate where both the abstract and the underlying document are prior art. Abstracts often are not written by the author of the underlying document and may be erroneous. It is our opinion that a proper examination under 37 CFR § 1.104 should be based on the underlying documents and translations, where needed. Accordingly, the preferred practice is for the examiner to cite and rely on the underlying document.

[Unpublished] When an examiner cites and relies only on an abstract, the applicant may wish to obtain a copy of the underlying document and submit a copy to the examiner when responding to a rejection relying on an abstract. In the event a reference is in a foreign language, if the applicant does not wish to expend resources to obtain a

translation, the applicant may wish to request the examiner to supply a translation. If

a translation is not supplied by the examiner, the applicant may wish to consider seeking supervisory relief by way of a petition (37 CFR § 1.181) to have the examiner directed to obtain and supply a translation.

[Unpublished] In the past, when neither the examiner nor the applicant relies on the underlying article, the board often expended the resources necessary to obtain a copy of the underlying scientific article, as well as translations thereof. When it did so, however, the burden of examining the application fell on the board in the first instance. Moreover, to the extent that the board relies on parts of a translation not previously provided to an applicant, any affirmance generally has to be a new ground of rejection under 37 CFR § 1.196(b)—which can result in further prosecution.

[Unpublished] In this case, we do not know whether the examiner or the applicant had or reviewed the underlying foreign language technical journal articles or translations thereof. The board cannot examine, in the first instance, all applications which come before it in an *ex parte* appeal under 35 U.S.C. § 134. In this particular appeal, we exercise discretion by declining to obtain translations of the underlying technical journal articles and thereafter evaluate on the merits in the first instance the translations. In our view, obtaining translations is the responsibility of the examiner. A review by the examiner and applicant of translations of the prior art relied upon in support of the examiner's rejection may supply additional relevant evidence as to whether there is a legally sufficient reason, suggestion, teaching or motivation to combine the teachings of the five technical journal articles. Moreover, an evaluation of translations may eliminate the need for an appeal.

C. Decision

[Unpublished] The decision of the examiner rejecting claims 38-39 under 35 U.S.C. § 103(a) over (1) Horner, (2) Suri, (3) Endel'man, (4) Manthey and (5) Ota is *vacated* and the application is *remanded*to the examiner. For the effect of a decision vacating an examiner's rejection, see *In re Zambrano*, 58 USPQ2d 1312 (Bd. Pat. App. &Int. 2001) (explaining that vacated rejection no longer exists).

[Unpublished] The examiner and/or the applicant may obtain translations of (A) Horner, (B) Endel'man and (C) Ota.

[Unpublished] Nothing in this opinion should be read as precluding the examiner from entering a rejection based on translations. In the event the examiner determines that claims 38-39 are unpatentable over the combination of the five references (or any additional prior art), then the examiner must identify and cite the specific portions (page and line or figure) of each article or prior art document upon which he relies in support of any rejection. We are primarily a board of review. Accordingly, neither the examiner nor applicant should expect in any further appeal for us to dig through five prior art references to come up with a theory which might support or negate a rejection in the first instance. Moreover, if the examiner enters a further rejection based on foreign language document, translations must be obtained if a further appeal is taken. We will not decide a further appeal without translations.

[Unpublished] We express no views on the ultimate merits of any rejection under 35 U.S.C. § 103(a) based on the five prior art references or any additional prior art which the

examiner and applicant may wish to make of record.

D. Order

[Unpublished] Upon consideration of the appeal, and for the reasons given, it is
[Unpublished] ORDERED that the examiner's rejection under §103(a) of claims 38-39 is *vacated.*
[Unpublished] FURTHER ORDERED that the application is *remanded* to the examiner for action not inconsistent with the views expressed in this opinion.
[Unpublished] FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

VACATED and REMANDED

Footnotes

2 To the extent these findings of fact discuss legal issues, they may be treated as conclusions of law.

- End of Case -

CURRICULUM VITAE

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Louisiana State University
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EDUCATION

B.S., Horticulture, Kansas State University, 1967

M.S., Pharmacology, Medical College of Wisconsin, 1976

Ph.D., Pharmacology, Medical College of Wisconsin, 1988

EXPERIENCE

2001-present	Associate Dean for Research and Graduate Studies Louisiana State University Health Sciences Shreveport, LA
July 2002-present	Professor, Department of Pharmacology and Therapeutics Louisiana State University Health Sciences Center Shreveport, LA
July 2002-present	Professor, Department of Anesthesiology Louisiana State University Health Sciences Center Shreveport, LA
2000-2001	Assistant Dean, School of Graduate Studies Louisiana State University Health Sciences Shreveport, LA
1997-2002	Associate Professor, Department of Pharmacology and Therapeutics Lousisana State University Health Sciences Center Shreveport, LA
1991 - 1997	Assistant Professor, Department of Pharmacology and Therapeutics Louisiana State University Medical Center Shreveport, LA
1989-1991	Postdoctoral Fellow, Department of Pharmacology University of Minnesota, Minneapolis, MN Advisor: Dr. Horace H. Loh

1988 -1989	Postdoctoral Fellow, Department of Pharmacology University of Minnesota, Minneapolis, MN Advisor: Dr. George L. Wilcox
1984 - 1987	Graduate Student, Department of Pharmacology and Toxicology Medical College of Wisconsin, Milwaukee, WI Advisor: Dr. James M. Fujimoto
1976-1984	Research Associate, Department of Pharmacology and Toxicology Medical College of Wisconsin, Milwaukee, WI Supervisor: Dr. James M. Fujimoto
1975-1976	Graduate Student, Department. of Pharmacology and Toxicology Medical College of Wisconsin, Milwaukee, WI Advisor: Dr. James M. Fujimoto
1972-1975	Research Technician, Department of Pharmacology Medical College of Wisconsin, Milwaukee, WI Supervisor: Dr. James M. Fujimoto
1969-1971	Research Technician, Biochemistry, AEC Plant Research Lab Michigan State University, East Lansing, MI Supervisor: Dr. Derek T.A. Lamport
1967-1969	Research Technician, Department of Biochemistry University of Kansas Medical Center, Kansas City, KS Supervisor: Dr. Dennis Diedrich, Dr. Santiago Grisolia
1965-1967	Research Technician, Horticulture, School of Agriculture Kansas State University, Manhattan, KS Supervisor: Dr. William Carpenter

SOCIETY MEMBERSHIPS

American Society for Pharmacology and Experimental Therapeutics
American Society for the Advancement of Science
Society for Neuroscience
American College of Clinical Pharmacology (Fellow)
International Narcotics Research Council

AWARDS

Tuition Scholarship, Medical College of Wisconsin, Graduate Studies Council, (1985-1986)
Travel Award, American Society for Pharmacology and Experimental Therapeutics, (1986)
Travel Award, Friends of Medical College of Wisconsin (1987)
Travel Award, Committee on Problems of Drug Dependence (1988)
Travel Award, American College of Neuropsychopharmacology (1988)

TEACHING

Student Conferences, General Pharmacology, Medical College of Wisconsin (1984-1987)

Lectures, General Pharmacology, School of Nursing, Medical College of Wisconsin (1984)

Teaching Assistant, Neuroscience Summer Workshop, Lake Itasca, University of Minnesota, (1988)

Medical Pharmacology Lectures and Student Conferences,
LSU Health Sciences Center (1991-present)

Clinical Pharmacology Conferences,
LSU Health Sciences Center (1992 - 1999)

Lectures in Graduate level courses:
Principles of Pharmacology I and II, Neurochemistry, Philosophical and Ethical Issues in Science, Behavioral Pharmacolgy, Neuropharmacology, Molecular Pharmacology, Integrative Structural Biology, Fundamentals of Biological Sciences
LSU Health Sciences Center (1992- present)

Course Director:
Principles of Pharmacology I, (1993-1996) Molecular Pharmacology (1996-2000) Clinical Pharmacology Conferences (1993 - 1998), LSU Health Sciences Center

Joint LSUHSC Physiology Department-Centenary College Summer Seminar Series
Lectures in Mentoring to undergraduate students (1996-present)

GRADUATE EDUCATION

Postdoctoral Fellows

Natalie Lenard, Ph.D., 2003-present

Guoqiang Guan, D.D.S., Ph.D., 2000-2002

Department of Pharmacology LSU Health Sciences Center Graduate Students

Research Advisor for: Zhong You Wei, Yaohui Li, Farzana Karim, Laura Tedesco, Scott Baker

Dissertation/Thesis committee member for: Ying Ye, Kehong Zhang, Pankaj Sikka, Donna Ross, James Hinson, Orlando Bueno, Alicia Chrisman, Yu Zhao, Troy Cenac, Olga Gurkovskaya, Rachell Romanoff

Students Graduated:

Zhong You Wei, M.S., 1995
Thesis title: Voltage-dependent calcium channels and G proteins in spinal morphine/clonidine synergistic antinociception

Yauhui Li, M.S., 1997
Thesis title: Alterations of Spinal Protein Kinase C Expression and Kinetics in Morphine Tolerance

Farzana Karim, Ph.D. 1999
Dissertation title: Functional aspects of opioid and alpha$_2$ adrenergic receptor activation: involvement of specific G proteins

Medical Student Summer Research Program

Students mentored:
Jeb Broyles (1993)
Eric Madore (1994)
Matthew Chamberlain (1996)
Joan Cheuk (1999)

Undergraduate and Teacher Summer Research Program

Students Mentored:
Lisa Walker (1994)
Chancy Burden (1998)
Kavita Belur (1997)

Multicultural Affairs "Jump-Start Program" for High School Students

Students Mentored:
Deana Rambo (summer 2000)

Other Student-Related Activities

Department of Pharmacology and Therapeutics Graduate Student Coordinator (1997-2000)

Organized LSUHSC-Shreveport Graduate Student Orientation (2000)

GRANT SUPPORT

Awarded as Principle Investigator

National Institute on Drug Abuse, Research Fellowship Award DA 05370 (Oct. 1, 1988-Sept. 30, 1991) - "Partial Characterization of Cloned Delta Opioid Receptor"

The Edward P.S. Stiles Trust Fund - LSUMC-S Institutional Funds, Young Investigator Award (Nov. 1, 1991 - Oct. 31, 1992) "Spinal Opioid and Adrenergic Analgesia in Opioid Tolerance" - $7,450. Renewed (Dec. 1, 1992 - Nov. 30, 1993) - $7,462

American Cancer Society Junior Investigator Award, Institutional support (May 1, 1992-June 30, 1993) "Identification of GTP-binding proteins which transduce spinal opioid receptor functions" - $6,000

Louisiana Education Quality Support Fund (July 1, 1993 - June 30, 1996) "Second messenger systems involved in opioid and alpha adrenergic interactions" - $144,976 - Approved

National Institutes on Drug Abuse, FIRST Award (May 1, 1993 -April 30, 1998) "Opioid and Alpha Adrenergic Agonist Interactions" - DA07972-$350,018

The Edward P.S. Stiles Trust Fund - LSUMC-S Institutional Funds, Bridging Award, "Opioid and Alpha Adrenergic Agonist Interactions" (January 1, 1999-December 30, 1999, $30,000)

National Institutes on Drug Abuse, RO3, DA12547, "Spinal nitric oxide in chronic inflammatory pain" (1/1/00-12/31/01) $100,000

Awarded as Contract for Program Project

National Institutes on Drug Abuse, Program Project, "Design of opioid analgesics devoid of tolerance/addiction", PI, Ping Law, University of Minnesota (6/1/02-5/30/07) $340,926

Awarded as Co-Investigator

National Institutes of Child Health and Development, RFA 9306, Pediatric Drug Evaluation Resource (9/30/93-9/30/98) Principle Investigator, John Wilson, M.D., Efficacy and pharmacokinetics of tramadol for treatment of pain in children, Sandra C. Roerig, Basic Investigator - $1,600,000

Submitted, October 1, 2001
National Institutes on Drug Abuse RO1 - "Spinal nitric oxide in chronic inflammatory pain" for 7/1/02-6/30/06, $500,000, not funded, will be resubmitted

SERVICE

GRANT REVIEWER

National Grant Reviews:

Study Sections:

ad hoc reviewer for SBIR applications, Molecular Biology Section - July 1998

ad hoc reviewer for IFCN-4, National Institutes of Health, October 14-16, 1998

ad hoc reviewer for NIH IFCN-7, SBIR Study section - April 2000, August 2001, March 2002, April 2003

Phone Reviews:

ad hoc reviewer for NIH (Tallarida) - October 1993

ad hoc reviewer for intramural grant at Allegany College, PA , 1997

ad hoc reviewer for EPSCoR grant application, March 1998

ad hoc reviewer for NIH IFCN-4, December 1998

Special Grant Reviewer for NIH, October 1995, December 1998, March 1999

ad hoc reviewer and chair of IFCN5-03 Study Section - October 2000

ad hoc reviewer for IFCN2 - December 2001

LSUHSC COMMITTEE SERVICE

1. Department of Pharmacology

1992, 1994, 2000	Pharmacology Faculty Search Committee	Member
1993, 1996, 2000	Qualifying Exam Committee	Member
1994	Faculty review of USMLE Step 1 (Nov. 17, 1993)	Member

2. LSUHSC - Shreveport

1994	Search Committee for Head, Dept. of Neurology	Member
1993-1997	Radiation Safety Committee	Member
1998- 2001	Ratiation Safety Committee	Chair
1997-1999, present	Admissions Committee	Member
1996	Reviewer of Cancer Center Applications	Member
1995-1998	Elected Faculty Council	Member
1997-1998	Elected Faculty Council	Chair
1995-1997, 2000	Research Advisory Committee	Member
1997-1999	Radioactive Drug Research Committee	Member
1998-1999	LCME Visit PreparationCommittee	Member
1999	Clinical Research Committee	Member
1999-present	Committee on Committees	Member
1999-present	Curriculum Committee	Member
2000-present	Committee to Draft Faculty Senate Bylaws	Member

3. LSUHSC - Faculty Senate for both campuses, Shreveport and New Orleans

1997-2001	LSUHSC - Shreveport Graduate School Representative	Member
1997-2001	Subcommittee for Faculty Welfare	Member
1999-2001	Representative to the Board of Supervisors	
2000-2001		Chair-elect

NATIONAL COMMITTEES

American Society for Pharmacology and Experimental Therapeutics
Subcommittee for Women in Pharmacology (1994-present)
Committee for Division of Education (2000-present)

Steering committee for 4th International Symposium on Imidazoline/Agmatine Systems
2001 - present

OTHER SERVICE

Director, Department of Pharmacology Seminar Program: LSU Medical Center (1993-1995)

Assistant Dean, School of Graduate Studies, LSUHSC-Shreveport, October 2000 - present

INVITED SEMINARS

Louisiana State University

1. Medical Center in Shreveport campus

   Department of Cell Biology and Anatomy - 1992

   Pathophysiology of Pain Symposium - 1993

   Department of Neurology Grand Rounds - 1995

   Clinical Pharmacology Interest Group -1996

   Department of Molecular and Cellular Physiology -1998

2. Shreveport campus (undergraduate)

   Seminars for the Department of Biology (1992-1996, 1999, 2001)

National

Department of Pharmacology, University of Texas Medical Center, Houston, TX (1993)

Department of Physiology, University of North Texas Health Sciences Center, Fort Worth, TX (1993)

Department of Pharmacology, University of Wisconsin - Madison, Madison, WI (1994)

Department of Pharmacology, Michigan State University, East Lansing, MI (1997)

Department of Pharmacology, University of Houston School of Pharmacy - Houston, TX (2000)

Department of Pharmacology, University of Arkansas Medical School - Little Rock, AR (2000)

OTHER PRESENTATIONS

June 7, 1997, Role of Protein Kinases in Spinal Morphine/Clonidine Antinociceptive Synergism, Pain Interest Group Meeting, Milwaukee, WI

CONTRIBUTIONS TO REFERRED PUBLICATIONS

1999 - present - Associate Editor, *Journal for Pharmacology and Experimental Therapeutics*

1994-1998 - Editorial Advisory Board, *Journal for Pharmacology and Experimental Therapeutics*

1995 - present - Editorial Borad, *Analgesia*

1990-present - reviewer for *Brain Research, Journal of Neurochemistry, Life Sciences, Brain Research Bulletin, Peptides, Proceedings of the Society for Experimental Biology and Medicine, Journal for Pharmacology and Experimental Therapeutics, Journal for Neuroscience. Pain, Free Radical Biology and Medicine, Neurochemistry International*

PUBLICATIONS

Roerig, S., Fujimoto, J.M., Wang, R.I.H., Isolation of hydromorphine and dihydromorphine glucuronides from urine of the rabbit after hydromorphine administration. *Proc. Soc. Expt. Biol. Med.* 143: 230-233 (1973)

Chatterjie, N., Fujimoto, J.M., Inturrisi, C.E., Roerig, S., Wang, R.I.H., Bowen, D., Field, F.H., and Clarke, D.D., Isolation and stereochemical identification of a metabolite of naltrexone from human urine. *Drug Metab. Disp.* 2: 401-405 (1974)

Fujimoto, J.M., Roerig, S., Wang, R.I.H., Chatterjie, N. and Inturrisi, C.E., Narcotic antagonist activity of several metabolites of naloxone and naltrexone tested in morphine dependent mice. *Proc. Soc. Expt. Biol. Med.*, 148: 443-448 (1975)

Lamport, D.T.A., Katona, L. and Roerig, S., Galactosylserine in extensin. *Biochem. J.*, 133: 125 (1976)

Roerig, S., Fujimoto, J.M., Wang, R.I.H., and Lange, D.G., Preliminary characterization of enzymes for reduction of naloxone and naltrexone in rabbit and chicken liver. *Drug Metab. Disp.* 4: 53-58 (1976)

Roerig, S.C., Fujimoto, J.M., and Wang, R.I.H., The stimulatory effect of morphine on metabolism of naloxone to 6α-naloxol in the guinea pig. *Drug Metab. Disp.* 5: 454-463 (1977)

Roerig, S.C., Fujimoto, J.M. and Wang, R.I.H., The stimulatory effect of morphine on reduction of naltrexone to 6α-naltrexol in the guinea pig. *Drug Metab. Disp.* 8:295-299 (1980)

Roerig, S.C., Christiansen, K.L., Jansen, M.A., Wang, R.I.H., Fujimoto, J.M., and Nickerson, M., Phylogenetic distribution of the hepatic enzyme system for reducing naloxone to 6α- and 6β-naloxol in vertebrates. *Comp. Biochem. Physiol.* 15: 93-97 (1980)

Lange, D.G., Roerig, S.C., Fujimoto, J.M. and Wang. R.I.H., Absence of cross-tolerance to heroin in morphine tolerant mice. *Science* 208: 72-74 (1980)

Lange, D.G., Roerig, S.C., Fujimoto, J.M. and Wang, R.I.H., Enhancement of etorphine brain concentrations and changes in etorphine-naloxone pA_2 values in morphine pretreated mice. *Biochem. Pharm.* 30: 147-155 (1981)

Lange, D.G., Roerig, S.C., Fujimoto, J.M. and Busse, L.W., Withdrawal tolerance and unidirectional non-cross tolerance in narcotic pellet implanted mice. *J. Pharmacol. Exp. Therap.*, 224: 13-20 (1983)

Brown, C.E., Roerig, S.C., Fujimoto, J.M. and Burger, V.T., The structure of morphine differs between the crystalline state and aqueous solution. *J. Chem. Soc., Chem Commun.* 1506-1508 (1983)

Roerig, S.C., O'Brien, S.M., Fujimoto, J.M. and Wilcox, G.L., Tolerance to morphine analgesia: decreased multiplicative interaction between spinal and supraspinal sites. *Brain Res.* 308: 360-363 (1984)

Brown, C.E., Roerig, S.C., Burger, V.T., Cody, R.B. and Fujimoto, J.M., Analgesic potencies of morphine 3- and 6-sulfates after intracerebroventricular administration in mice: relationship to structural characteristics defined by mass spectrometry and nuclear magnetic resonance, *J. Pharm. Sci.*, 74: 821-824 (1984)

Roerig, S.C., Fujimoto, J.M., Franklin, R.B. and Lange, D.G., Unidirectional non-cross tolerance (UNCT) in rats and an apparent dissociation between narcotic tolerance and physical dependence. *Brain Res.* 327: 91-96 (1985)

Roerig, S.C., Fujimoto, J.M. and Lange, D.G., Development of tolerance to respiratory depression in morphine- and etorphine-pellet-implanted mice. *Brain Res.*, 400: 278-284 (1987)

Roerig, S.C., Arteau, C. and Fujimoto, J.M., Antagonism by nalmefene of systemic and intrathecal morphine-induced analgesia in mice. *Proc. Soc. Expt. Biol. Med.*, 186: 234-239 (1987)

Roerig, S.C., Fujimoto, J.M. and Tseng, L.F., Comparisons of descending pain inhibitory pathways activated by ß-endorphin and morphine as characterized by supraspinal and spinal analgesic interactions in mice. *J. Pharmacol. Exp. Ther.* 247: 1107-1113 (1988)

Roerig, S.C. and Fujimoto, J.M., Morphine analgesia in different strains of mice: relationship of supraspinal-spinal multiplicative interaction to tolerance. *J. Pharmacol. Exp. Ther.* , 247: 603-608 (1988)

Roerig, S.C. and Fujimoto, J.M., Multiplicative interaction between intracerebroventricularly and intrathecally administered morphine for analgesia in mice: involvement of mu, delta and kappa receptors. *J. Pharmacol. Exp. Ther.* 249: 762-768 (1989)

Rady, Jodie J., Roerig, Sandra C. and Fujimoto, James M., Heroin acts on different opioid receptors than morphine in Swiss Webster and ICR mice to produce antinociception, *J. Pharmacol. Exp. Ther.* 256: 448-457 (1991)

Roerig, S.C., Hoffman, R.G., Takemori, A.E., and Fujimoto, J.M., Isobolographic analyses of analgesic interactions between intracerebroventricularly and intrathecally administered opioid agonists: morphine, fentanyl and D-Ala^2-D-Leu^5-enkephalin. *J. Pharmacol. Exp. Ther.* , 257: 1091-1099 (1991)

Roerig, Sandra C., Loh, H.H. and Law, P.Y., Requirement of ADP-ribosylation for the pertussis toxin-induced alteration in electrophoretic mobility of G-proteins. *Biochem. Biophys. Res. Comm.*, 180:1227-1232 (1991)

Roerig, S.C., Lei, S. Kitto, K, Hylden, J.K.L. and Wilcox, G. L., Interactions between spinally administered opioid and noradrenergic agonists in the substance P test in mice: multiplicitivity involves δ and alpha$_2$ receptors. *J. Pharmacol Exp. Ther.*, **262**: 365-374 (1992)

Roerig, Sandra C., Law, P.Y. and Loh, H.H., Identification of three separate guanine nucleotide-binding proteins which interact with the δ opioid receptor in NG108-15 neuroblastoma x glioma hybrid cells. *Mol. Pharm.*, **41**: 822-831 (1992)

Dujic, Z., Marijic, J., Roerig, S. C., Dujic, J., Kampine, J. P. and Bosnijak, Z., Presnyaptic modulation of acetylcholine release from the cat stellate ganglion by morphine, *Croatian Med. J.*, **34**: 33-42 (1993)

Saphier, D., Roerig, S.C., Ito, C., Vlasak, W.R., Farrar, G.E., Broyles, J.E. and Welch, J.E., Inhibition of neural and neuroendocrine activity by α-interferon: neuroendocrine, electrophysiological and biochemical studies in the rat, *Brain, Behav Immun.*, **8**:37-56 (1994)

Roerig, Sandra C. , Decreased spinal morphine/clonidine antinociceptive synergism in morphine-tolerant mice, *Life Sci*, **56**: PL115-PL122 (1995)

Roerig, Sandra C., Cynthia L. Williams, Victor J. Hruby, Thomas F. Burks and Gary Rosenfeld, Inhibition of adenylyl cyclase activity by the cholesyctokinin analog SNF9007 in neuroblastoma x glioma NG108-15 hybrid cells, *Reg. Peptides*, **61**: 51-56 (1996)

Wei, Zhong you, Farzana Karim and Sandra C. Roerig, Spinal morphine/clonidine anticociceptive synergism: involvement of G proteins and N-type voltage-dependent calcium channels, *J. Pharm. Exp. Therap.* **278**:1392-1407 (1996)

Roerig, Sandra C. and Kurt Howse, ω-Agatoxin IVA blocks spinal morphine/clonidine antinociceptive synergism, *Eur. J. Pharmacol.*. **314**:293-300 (1996)

Wei, Zhong you and Sandra C. Roerig, Spinal morphine/clonidine antinociceptive synergism is regulated by protein kinase C, but not protein kinase A activity, *J. Pharmacol. Exp. Therap.* **287**:937-943 (1998)

Li, Yaohui and Sandra C. Roerig, Alteration of Spinal Protein Kinase C Expression and Kinetics in Morphine. but not Clonidine Tolerance, *Biochem Pharmacol.*, **58**:493-501 (1999)

Roerig, Sandra C., Timothy Busch and Yaohui Li, Decreased spinal morphine/clonidine antinociceptive synergism in clonidine-tolerant mice, *Analgesia*, 4:187-195 (1999)

Napier, Leslie D., Sandra C. Roerig, Darice A. Yoshishige, Barbara A. Barron and James L. Caffrey, Canine cardiac muscarinic receptors, G-proteins and adenylate cyclase following chronic morphine, *J. Pharmacol. Exp. Ther.*, **291**: 725-732 (1999)

Zavecz, James, H., Harold D. Battarbee, Orlando Bueno, Ronald E. Maloney, Sandra C. Roerig and James M. O'Donnell, Down regulation of cardiac L-type Ca^{2+} channels in the portal hypertensive rat *Amer. J. Physiol.*, 279:G28-G39 (2000)

Karim, Farzana and Sandra C. Roerig, Differential effects of antisense oligodeoxynucleotides directed against $G_{z\alpha}$ and $G_{o\alpha}$ on antinociception produced by spinal opioid and α_2 adrenergic receptor agonists (*Pain*, **87** 181-191, 2000)

Tedesco, Laura, John Fuseler, Matther Grisham, Robert Wolf and Sandra C. Roerig, Nitric oxide synthase inhibitors reverse hyperalgesia but not inflammation in a rat model of chronic arthritis *Pain*, **95**: 215-223, 2002

Roerig, Sandra C., Spinal and supraspinal agmatine activate different receptors to enhance spinal morphine antinociception (submitted, *J. Pharmacol. Exp. Ther.*)

Karim, Farzana, Paul Prather and Sandra C. Roerig, Opioid and alpha$_2$-adrenergic receptor agonists enhance incorporation of [α-^{32}P] GTP azidoanilide into spinal G proteins (submitted, *Biochem. Pharm.)*

ABSTRACTS

Lamport, D.T.A., Katona, L. and Roerig, S., Amino acid sequence of hydroxyproline-rich tryptic peptides from acid-stripped primary cell walls. *Fed. Proc.* 30: 1317 (1971)

Lange, D.G., Fujimoto, J.M., Roerig, S.C. and Wang R.I.H., Morphine induced sensitization to naloxone: enhanced disposition of naloxone to the brain. *The Pharmacologist*, 16: (1974)

Lange, D.G., Fujimoto, J.M., Roerig, S. and Wang, R.I.H., The Effect of morphine on the metabolism of naloxone. National Drug Abuse Conference (1976)

Fujimoto, J.M., Roerig, S.C. and Wang, R.I.H., Reduction of naloxone by the guinea pig. *Fed. Proc.* 34: 487 (1976)

Roerig, S., Fujimoto, J.M., Nickerson, M. and Wang, R.I.H., A preliminary comparison of the liver enzyme systems for reducing naloxone to 6α-and 6β-naloxol. Abstracts of Papers, Soc. of Toxicol., 15th Annual Meeting, 87 (1976)

Roerig, S., Fujimoto, J.M. and Wang, R.I.H., Stimulation of morphine on metabolism of naloxone to 6α-naloxol in the guinea pig. *The Pharmacologist*, 18: 121 (1976)

Roerig, S.C., Fujimoto, J.M. and Wang, R.I.H., Effect of morphine on naltrexone metabolism in the guinea pig. *The Pharmacologist*, 20: 546 (1978)

Fujimoto, J.M., Lange, D.G., Roerig, S.C. and Wang, R.I.H., Development of differential tolerance to narcotic agonists by etorphine pellet implantation in mice. *The Pharmacologist*, 21: 79 (1979)

Roerig, S.C., Fujimoto, J.M. and Lange, D.G., Separation of expression of narcotic tolerance from physical dependence in rats. *The Pharmacologist*, 21:439 (1976)

Lange, D.G., Fujimoto, J.M., and Roerig, S.C., Continuous intraventricular infusions of narcotic agonists does not alter analgesic potency of systemically administered narcotics. *The Pharmacologist*, 21: 440 (1976)

Roerig, S.C., Lange, D.G., Wang, R.I.H., and Fujimoto, J.M., Differences in withdrawal tolerance ED50 values for several narcotics in etorphine pelleted mice. *The Pharmacologist*, 22: 786 (1980)

Roerig, S.C., Lange, D.G., and Fujimoto, J.M., Comparison of tolerance to respiratory depression from morphine (M), etorphine (E) and heroin (H) in morphine pellet implanted mice. *The Pharmacologist*, 23: 115 (1981)

Roerig, S.C., Lange, D.G. and Fujimoto, J.M., Tolerance to the potent narcotic analgesic morphine-6-ethereal sulfate (M6ES) in mice. *The Pharmacologist*, 24: 126 (1982)

Roerig, S.C., Lange, D.G., and Fujimoto, J.M., Tolerance development in morphine pellet implanted mice to intrathecally administered delta but not mu receptor agonists. *Fed. Proc.* 43: 968 (1984)

Brown, C.E., Roerig, S.C., Fujimoto, J.M. and Burger, V.T. CP/MAS 13C NMR spectral evidence of long-range substituent effects in rigid opiates. *Fed. Proc.* 42(7): A2056 (1983) (Amer. Soc. Biol. Chemists)

Brown, C.E., Roerig, S.C., Fujimoto, J.M. and Burger, V.T. CP/MAS 13C NMR spectral evidence of long-range substituent effects in rigid opiates. International Magnetic Resonance meeting (Aug, 1983)

Roerig, S.C., O'Brien, S.M. and Fujimoto, J.M., Morphine analgesic tolerance: decreased synergistic interaction between spinal and supraspinal sites in morphine pellet (MP) implanted mice. *Fed. Proc.* 43(4): 968 (1984)

Roerig, S.C., O'Brien, S.M. and Fujimoto, J.M., Tolerance to morphine hot plate analgesia (HPA): decrease in synergism between spinal (S) and supraspinal (SS) sites. *The Pharmacologist,* 26: 14 (1984)

Roerig, S.C., O'Brien, S.M. and Fujimoto, J.M., Basis for lack of analgesic cross tolerance to heroin (H) in morphine (M) tolerant mice. IUPHAR 9th International Congress of Pharmacology, 1549P (1984)

Roerig, S.C. and Fujimoto, J.M., Analgesic synergism between intracerebroventricular (ICV) and intrathecal morphine sulfate remains unaltered after ICV 6-hydroxydopamine. *Fed. Proc.* 44(5): 1721 (1985)

Roerig, S.C., Majest, S.M. and Fujimoto, J.M., Differential sensitivity to naloxone HCl (N) between spinal and supraspinal sites in mice. *The Pharmacologist*, 27: 117 (1985)

Brown, C.E., Roerig, S.C., Burger, V.T., Cody, R.B. and Fujimoto, J.M., Analgesic potencies of morphine 3- and 6-sulfates after intracerebroventricular administration in mice: relationship to structural characteristics defined by laser desorption/fourier transform mass spectrometry and nuclear magnetic resonance. *The Pharmacologist*, 27: 275 (1985)

Roerig, S.C. and Fujimoto, J.M., Intrathecal 6-hydroxydopamine (6-OHDA) treatment decreases morphine analgesic synergism between spinal and supraspinal sites in mice. *Fed. Proc.* 45: 666 (1986)

Fujimoto, J.M, Roerig, S.C., and Arteau, C., Narcotic antagonist activity of nalmefene on peripheral and spinal morphine analgesia. *Fed. Proc.* 45: 667 (1986)

Roerig, S.C., Arteau, C. and Fujimoto, J.M., Spinal delta and kappa but not mu opiate receptors involved in spinal-supraspinal morphine synergism. *The Pharmacologist*, 28: 96 (1986)

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COMMENTS FOR AUTHOR

To Reviewer #1
Associate Editor: Sandra C. Rorig, Ph.D.

Manuscript (MS) #: JPET/2000/002825

MS Title: Analgesic Synergy between Topical Lidocaine and Topical Opioids

Authors: Yuri A. Kolesnikov, Igor Chershnev, and Gavril W. Pasternak

INSTRUCTIONS FOR REVIEWER

1. When you have completed your review, please divide your comments into:
   a) Comments for Editor - Please type directly onto the pink sheet.
   These comments will not be sent to the author.
   Comments regarding acceptability must be confined to the pink sheet.
   b) Comments for Author - Please type directly onto this yellow sheet.
   These comments should be constructive without indicating acceptability of the manuscript.

COMMENTS: **Date Reviewed:** 5/19/00

The manuscript entitled "Analgesic synergy between topical lidocaine and topical opioids" (MS#002825) by Kolesnikov et al. describes the potential for further development of topical combination therapy for pain relief. The primary advantage of this treatment is the theoretical absence of side effects that can be problematic with most other forms of opioid administration. The synergistic effects were so profound, one wanted to know if the side effects really WERE absent under these conditions and whether tolerance would develop as rapidly to this drug combination as it might to the effect of a single drug. Obviously, those questions weren't asked in these studies, but it would be nice if there were some discussion of them in terms of practical uses for this approach. More specifically germane to the results from this study:

1. Did naloxone therapy have any effect on lidocaine analgesia alone?
2. Referring to Fig. 3A and its discussion in the text, was the naloxone administered in the same dose, by the same route and at the same time as was indicated in Fig. 5? This should be stated. More importantly, the authors state that the synergistic analgesic effect of lidocaine/morphine was significantly blocked by naloxone, but they don't say how much; the % of animals remaining analgesic after naloxone should be stated.
3. In fig.5, lidocaine curves are included in both graphs and appear to be the same. At some point in this paper the authors should show the effects of naloxone alone in this paradigm. One spot would be to exclude lidocaine from one of these graphs and insert the naloxone curve instead.
4. On page 11 the authors state, "The activity of levorphanol and buprenorphine extends the activity of opioid systems beyond mu receptors." Are they referring to opioid systems active topically? They've already shown other opioid receptor subtype systems are active after peripheral and central administration. Additionally, while Levorphanol does elicit actions through non-μ opioid receptors, the results from these studies don't really address that point. The fact that a single dose of naloxone totally blocked lidocaine/Levorphanol analgesia suggests that Levorphanol was acting solely through μ receptors, since κ_3 analgesia is less sensitiv to naloxone. In the absence of more selective μ antagonist treatments (e.g. β-FNA), the authors should avoid making such blanket statements.

Journal of Pharmacology and Experimental Therapeutics

Reviewer #2
Associate Editor: Dr. Roerig

MS #: JPET/2000/002825

MS Title: Analgesic synergy between topical lidocaine and topical opioids

Authors: Koesnikov, Chershnev and Pasternak

This article is an extension of recently-completed studies performed by the authors examining the analgesic responses following topical administration of opioids in connection with other pharmacological agents. In this study, the authors perform straightforward and quite unambiguous demonstrations that topical lidocaine and topical opioids each produce analgesic responses alone, and display quite marked synergy following combined administration. It is very surprising given the advanced state of the field of analgesia that such studies have never been performed previously, but the authors conclusively demonstrate this important property of both drug classes. There are a number of comments and issues that should be addressed.

1. p. 3, line 8: "...lidocaine with a low dose of an opioid...

2. p. 6: Topical administration: The authors should provide a 1-sentence rationale as to why a DMSO solution was used.

3. p. 8, results and Figure 1a: Indicate what dose of lidocaine was used in this particular initial experiment.

4. p. 9, lines 1 and 2: What dose and route of naloxone was used to reverse the analgesic effects of lidocaine and morphine?

5. p. 11, line 3: delete "an".

6. p. 11, line 10: "All of the opioids..."

7. p. 11, 1st sentence of third paragraph: The sentence does not make sense as presently constructed.

8. p. 12, line 11: "resulted from its receptor selectivity..."

9. p. 12, line 14: "...study. It will be of interest..."

10. The paper is devoid of any statistical data; it is up to the Editor if such additional data are necessary.

Minor points:

1. Page 5, line 3 should read "housed" instead of "housing."
2. Page 12, line 12 - remove the word "get."
3. Page 12, line 14 - add the word "be" - "it will be of interest..."
4. Fig. 5A legend, line 4 should read "application was tested in the tailflick assay."
5. Fig. 6A, Y-axis label misspelled.
6. Fixed ratios listed in Fig. 6 legend do not jive with fixed ratios given in Table 1 - which is correct? Also, Fig. 6A legend should be in reference to lidocaine/Levorphanol ratio, not buprenorphine.

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Analgesic Synergy between Topical Lidocaine and Topical Opioids[1]

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ABSTRACT

Topical drugs avoid many of the problematic side effects of systemic agents. Immersion of the tail of a mouse into a solution of dimethyl sulfoxide (DMSO)-containing morphine produces a dose-dependent, naloxone-sensitive, analgesia (ED_{50} 6.1 mM; CL 4.3, 8.4) limited to the portion of the tail exposed to the drug. DMSO alone in this paradigm had no analgesic activity. Like morphine, the opioids levorphanol (ED_{50} 5.0 mM; CL 3.8, 7.8) and buprenorphine (ED_{50} 1.1 mM; CL 0.7, 1.5) were effective topical analgesics. Lidocaine also was active in the tail-flick assay (ED_{50} 2.5 mM; CL 2.0, 3.4), with a potency greater than morphine. As expected, the free base of lidocaine was more potent than its salt. Combinations of a low dose of lidocaine with a low dose of an opioid yielded significantly greater than additive effects for all opioids tested. Isobolographic analysis confirmed the presence of synergy between lidocaine and morphine, levorphanol and buprenorphine. These studies demonstrate a potent interaction peripherally between opioids and a local anesthetic and offer potential advantages in the clinical management of pain.

Topical treatments offer many advantages over systemic drugs. By limiting the exposure of a drug to the periphery, central side effects can be markedly reduced. For opioids, this might decrease limiting side effects, such as sedation, respiratory depression, and nausea. Further limiting the drug to the actual site of action has even more advantages, by avoiding peripherally mediated side effects, such as constipation. In earlier studies, we demonstrated the activity of topical morphine in the radiant heat tail-flick assay after immersion in a dimethyl sulfoxide (DMSO) solution (Kolesnikov and Pasternak, 1999a). The analgesic actions seen with topical morphine were limited to the region of the tail exposed to the drug and were not seen in more proximal areas not exposed to the drug. DMSO alone was inactive in this paradigm. Other opioid ligands acting through kappa and delta receptors have activity peripherally in the radiant heat tail-flick assay as well (Kolesnikov et al., 1996a; Kolesnikov and Pasternak, 1999b). Thus, topical opioids might be useful in pain control.

Synergy is important in opioid action. First described between supraspinal and spinal sites (Yeung and Rudy, 1980), it has also been described between brainstem nuclei (Rossi et al., 1993) and between peripheral and central sites (Kolesnikov et al., 1996b). Synergy has been observed between opioids of different classes (Horan et al., 1992; Adams et al., 1993; Rossi et al., 1994; He and Lee, 1998).

Opioid actions also can be modulated by nonopioid classes of drugs. For example, opioid tolerance can be prevented or reversed by *N*-methyl-D-aspartate (NMDA) antagonists (Trujillo and Akil, 1991; Ben-Eliyahu et al., 1992; Tiseo and Inturrisi, 1993; Elliott et al., 1994) and nitric oxide synthase inhibitors (Kolesnikov et al., 1992, 1993). Unfortunately, NMDA antagonists have proven difficult to use systemically due to their profound psychomimetic and dysphoric actions. These problems might be avoided by a topical approach. We were able to demonstrate in our topical paradigm that the combination of an NMDA antagonist with an opioid blocked tolerance to the opioid (Kolesnikov and Pasternak, 1999a,c). This activity of NMDA antagonists topically presumably would avoid the limiting side effects that preclude their use systemically.

Lidocaine, a local anesthetic, is active topically, by blocking sodium channels, a mechanism distinct from the opioids (Woosley and Funck-Brentano, 1988). Clinical studies have shown advantages to the combination of intrathecal lidocaine and opioids (Atanassoff et al., 1997; Saito et al., 1998a,b), leading us to question whether similar advantages might be seen topically. We therefore have examined the activity of topical lidocaine in the tail-flick assay alone and in combination with a number of opioids.

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ABBREVIATIONS: DMSO, dimethyl sulfoxide; NMDA, *N*-methyl-D-aspartate; CL, confidence limits.

Mat rials and M thods

Male Crl:CD-1(ICR)BR mice (25–30 g; Charles River Breeding Laboratory, Bloomington, MA) were maintained on a 12-h light/dark cycle with food and water available ad libitum. Mice were housed in groups of five until testing. Opioids were generously provided by the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD). Lidocaine was purchased from Sigma Chemical Co. (St. Louis, MO). Lidocaine base was used in all experiments unless indicated otherwise.

Topical Administration. Drugs were administered topically and analgesia assessed as previously described (Kolesnikov and Pasternak, 1999a). In this procedure, the distal portion of the tail (2–3 cm) is immersed in a DMSO solution containing the indicated drugs for the stated time, typically 2 min (Kolesnikov and Pasternak, 1999a). Prior studies have documented that DMSO alone has no effect when tested in this manner in the radiant heat tail-flick assay (Kolesnikov and Pasternak, 1999a). Furthermore, DMSO provides an effective way of solubilizing a wide range of drugs and facilitating their transport through the skin. The onset of analgesia is rapid, with peak effects seen immediately after the removal of the tail from the treatment solution. Therefore, we tested animals immediately after termination of topical administration.

Radiant Heat Tail-Flick Test. Testing was performed on the portion of the tail immersed in the treatment solution, because the analgesic actions of agents administered in this manner are restricted to the exposed portions of the tail; proximal regions are not affected (Kolesnikov and Pasternak, 1999a). Antinociception, or analgesia, was defined quantally as a tail-flick latency for an individual animal that was twice its baseline latency or greater. Baseline latencies typically ranged from 2.5 to 3.0 s, with a maximum cutoff latency of 10 s to minimize tissue damage in analgesic animals. Group comparisons were performed with the Fisher's exact test. ED_{50} values were determined with the Bliss program (Finney, 1976; Umans and Inturrisi, 1981), as previously reported (Kolesnikov et al., 1999a).

Drug Interactions. Isobolographic analysis was used to determine drug interactions (Talaradia et al., 1997). ED_{50} values were determined for each agent alone. They were then tested together at various doses at a constant ratio based on their respective ED_{50} values. In the figures, all points represent ED_{50} values. Values on the axes represent the ED_{50} values for the indicated drug alone, and the line connecting them corresponds to simple additive interactions. Points lying below the line of additivity indicate synergism. Significance was assumed by the lack of overlap of the confidence limits of the combination value with the confidence limits of the line of additivity.

Results

Topical Lidocaine and Morphine Interactions. First, we assessed the activity of topical lidocaine using the same administration paradigm previously shown active for opioids and NMDA antagonists (Kolesnikov and Pasternak, 1999a). Earlier studies emphasized the importance of exposure time in the activity of morphine. Similarly, the analgesic response to lidocaine was dependent on the exposure time (Fig. 1A). The response from a constant concentration of lidocaine increased from 20% at 30 s to 70% at 2 min. Time action curves revealed a maximal response immediately after removal of the tail from the solution, with a gradual decrease to baseline levels within 20 min (Fig. 1B). This response was slightly shorter in duration than a morphine dose giving the same maximal response. A lower lidocaine dose gave both a decreased maximal response and a shorter duration of action.

Both the free base and salt of lidocaine were examined

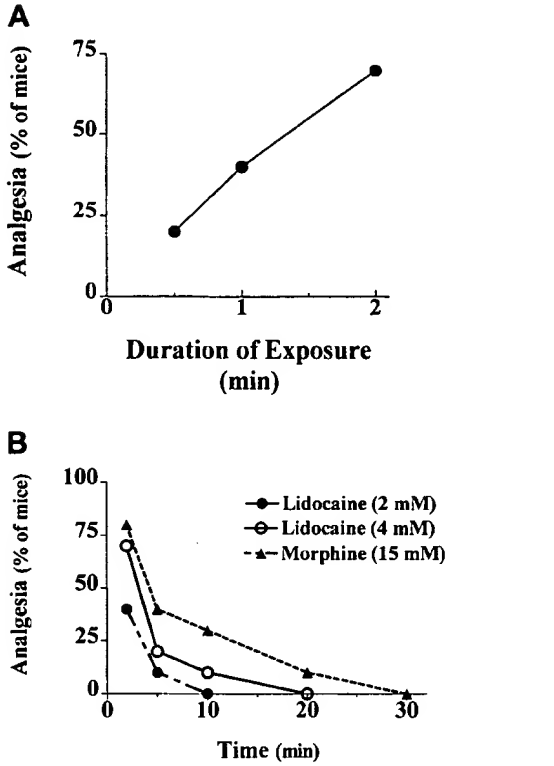

Fig. 1. Time dependence of topical lidocaine analgesia. A, groups of mice ($n \geq 10$) were exposed to a fixed concentration of topical lidocaine (4.3 mM) for 30 s, 1 min, and 2 min and then were tested in the tail-flick assay immediately after termination of drug exposure. B, groups of mice ($n \geq 10$) were treated with lidocaine (4.3 or 2.15 mM) or morphine (15 mM) for 2 min and then tested in tail-flick assay at the indicated time over 30 min.

(Fig. 2). Both were active, but the salt was less effective and plateaued at a 50% to 60% response. As expected, the free base form of lidocaine was more active, achieving a 75% response. However, it displayed a biphasic dose-response curve, with increases in concentration beyond 20 mM revealing a progressive lowering of analgesic activity. Morphine also was active, as previously reported (Kolesnikov and Pasternak, 1999a), with a potency intermediate between the two

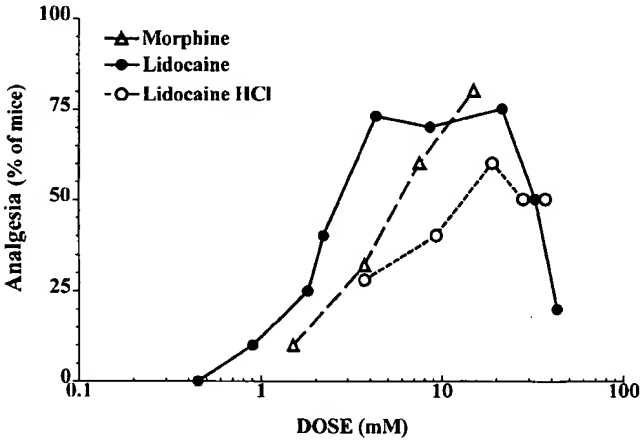

Fig. 2. Effects of topical lidocaine and morphine. Groups of mice ($n \geq 10$) were exposed to the indicated concentration of the free base of lidocaine, lidocaine HCl, or morphine for 2 min and tested immediately afterward.

TABLE 1

Analgesic potency of lidocaine and opioids alone and in combination

ED_{50} values were determined from dose-response curves and presented with 95% confidence limits. For lidocaine, the ED_{50} value was determined only from the initial portion of the curve. Combinations were also examined using increasing doses of a fixed ratio of the indicated drugs. ED_{50} values were determined and presented with the 95% confidence limits. The relative potency of the various drugs in combination were compared with the same drug alone as a ratio. The fixed ratios were as follows: lidocaine/morphine, 0.5; lidocaine/buprenorphine, 2.4; lidocaine/levorphanol, 0.5.

Treatment	Lidocaine		Opioid	
	ED_{50} Value	Ratio	ED_{50} Value	Ratio
	mM		*mM*	
Lidocaine alone	2.5 (2.0, 3.4)			
Morphine alone			6.1 (4.3, 8.4)	
Buprenorphine alone			1.1 (0.7, 1.5)	
Levorphanol alone			5.0 (3.8, 7.8)	
Lidocaine/morphine	0.85 (0.6, 1.1)	2.9	1.7 (1.2, 2.2)	3.6
Lidocaine/levorphanol	0.47 (0.3, 0.8)	5.3	0.94 (0.6, 1.6)	5.3
Lidocaine/buprenorphine	0.44 (0.3, 0.6)	5.7	0.18 (0.12, 0.240)	6.1

forms of lidocaine (Table 1). The antagonist naloxone given alone was without effect.

Initially we assessed potential interactions between lidocaine and morphine using a fixed, low dose of each (Fig. 3A). Alone, lidocaine and morphine produced peak responses of only 20%. Together, their peak response was 80%, far greater than anticipated from simple additive interactions ($P < .004$). Comparing the areas under the curve gave even more dramatic differences. As anticipated, naloxone (1 mg/kg, s.c.), given 20 min before agonist treatment, completely reversed the effects of the combination (data not shown).

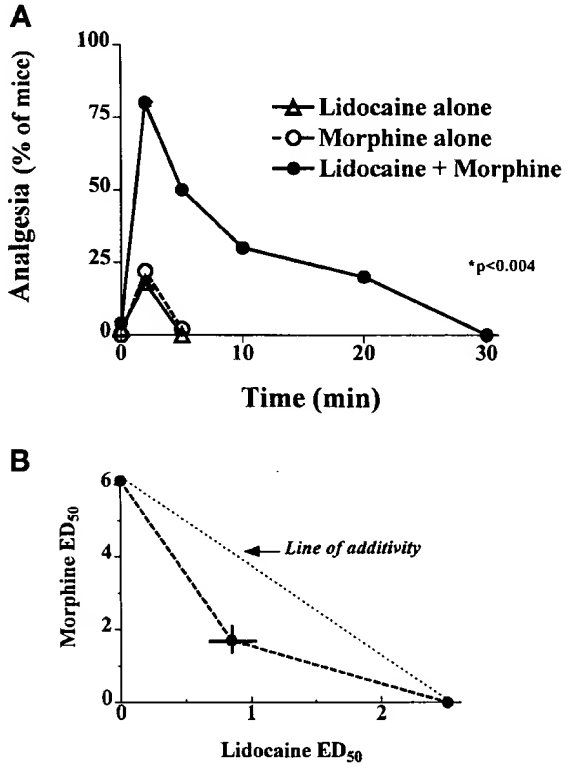

Fig. 3. Topical lidocaine and morphine interactions. A, groups of mice received either topical morphine (1.5 mM; $n = 10$) or lidocaine (0.9 mM; $n = 10$) alone or both together ($n = 20$). The combination was significantly ($P < .004$) more active at peak effect than the sum of two individual agents. B, using a fixed lidocaine/morphine ratio of 0.5, the ED_{50} value of combination was determined with the 95% confidence limits. The presence of the ED_{50} value below the line of additivity indicates the presence of synergy, confirmed by the lack of overlap between the 95% confidence limits for the drugs.

To further assess the possibility of synergy, we next employed isobolographic analysis (Tallarida et at., 1997). A dose-response curve was generated using increasing doses of a fixed ratio of lidocaine/morphine. The ED_{50} value fell well below the line of additivity, indicating synergism (Fig. 3B). The lack of overlap of the confidence limits of the combination value with those of the line of additivity confirmed its significance.

We also explored the relationship of lidocaine and morphine combinations by defining the ED_{50} values of each agent alone and in combination with a fixed dose of the other rather than a ratio (Table 2). Low doses of morphine with little activity alone markedly enhanced the potency of lidocaine. The effect seemed to plateau, with little advantage seen by increasing the morphine concentration from 3 to 4.5 mM. Similar results were seen with the morphine dose-response curves. Again, a low dose of lidocaine facilitated morphine analgesia, with little additional effect seen after doubling the lidocaine concentration from 0.9 to 1.8 mM. Thus, the enhanced activity of the combination of the drugs was most evident at low concentrations of each.

Topical Lidocaine and Other Opioids. We next explored whether the synergy seen with morphine/lidocaine combinations extended to other opioids with other receptor mechanisms of action, including levorphanol and buprenorphine. Topically, levorphanol and buprenorphine both yielded full analgesic responses, with ED_{50} values of 5.0 and 1.1 mM, respectively (Fig. 4; Table 1).

TABLE 2

Effects of fixed doses of morphine or lidocaine on the others analgesic potency

ED_{50} values with 95% confidence limits were determined from at least three doss of topical lidocaine alone or with the indicated morphine concentration, or with topical morphine alone or with the indicated concentration of lidocaine.

	ED_{50}	95% Confidence Limits	Shift
	mM		
Lidocaine alone	2.5	(2.0, 3.4)	
+Morphine 1.5 mM	1.0	(0.4, 1.8)	2.5
+Morphine 3.0 mM	0.8	(0.6, 1.1)	3.1
+Morphine 4.5 mM	0.7	(0.5, 0.9)	3.6
Morphine alone	6.1	(4.3, 8.4)	
+Lidocaine 0.45 mM	3.6	(2.6, 4.5)	1.7
+Lidocaine 0.9 mM	1.5	(0.9, 2.6)	4.1
+Lidocaine 1.8 mM	1.3	(0.6, 1.3)	4.7

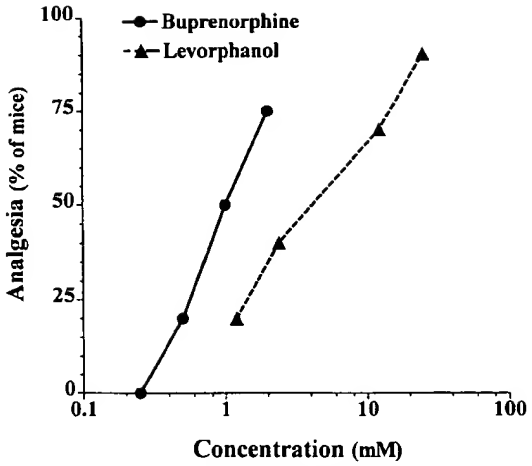

Fig. 4. Effects of topical buprenorphine and levorphanol. Groups of mice ($n \geq 10$) were exposed to the indicated concentration of the drug for 2 min and were tested immediately afterward.

Combinations of low doses of lidocaine and these opioids gave greater than additive analgesic actions (Fig. 5). The results with levorphanol closely resembled those of morphine, with the combination of low lidocaine and levorphanol doses giving a maximal response far beyond that expected by simple additive interactions ($P < .03$) as well as a prolonged duration far exceeding that of either alone (Fig. 5A). Although each drug alone had no effect beyond 5 min, together their response lasted for greater than 20 min. The effects of the combination of doses were readily antagonized by naloxone. The response to lidocaine alone (2.5 mM) was insensitive to naloxone (1 mg/kg, s.c.). (Data not shown.)

Buprenorphine and lidocaine gave similar results. The maximal responses of the two together were far beyond those anticipated by simple additive interactions (Fig. 5B). The duration of the response of the combination also markedly differed from that of either agent alone. Alone, each drug lasted less than 10 min. In contrast, the duration of the response of the combination was quite prolonged. The peak effect of the combination was 80% and persisted for 10 min. Analgesia could still be demonstrated after 45 min. Indeed, the duration of the response from the lidocaine/buprenorphine combination exceeded that seen with any of the other opioids tested. Naloxone significantly lowered the response of the combination.

Isobolographic Analysis of Lidocaine/Opioid Interactions. We next examined the combinations of the additional opioids isobolographically using dose-response curves with fixed ratios of the two drugs in combination (Fig. 6; Table 1). Combining levorphanol with lidocaine enhanced their relative potencies over 5-fold, which was more than the enhancement of morphine by lidocaine. Isobolographic analysis was consistent with synergy (Fig. 6A). Buprenorphine and lidocaine together shifted their individual ED_{50} values approximately 6-fold. Again, isobolographic analysis indicated synergy (Fig. 6B).

Discussion

Lidocaine is a widely used local anesthetic (Woosley and Funck-Brentano, 1988). It acts through the blockade of sodium channels, a mechanism distinct from the opioids. In the

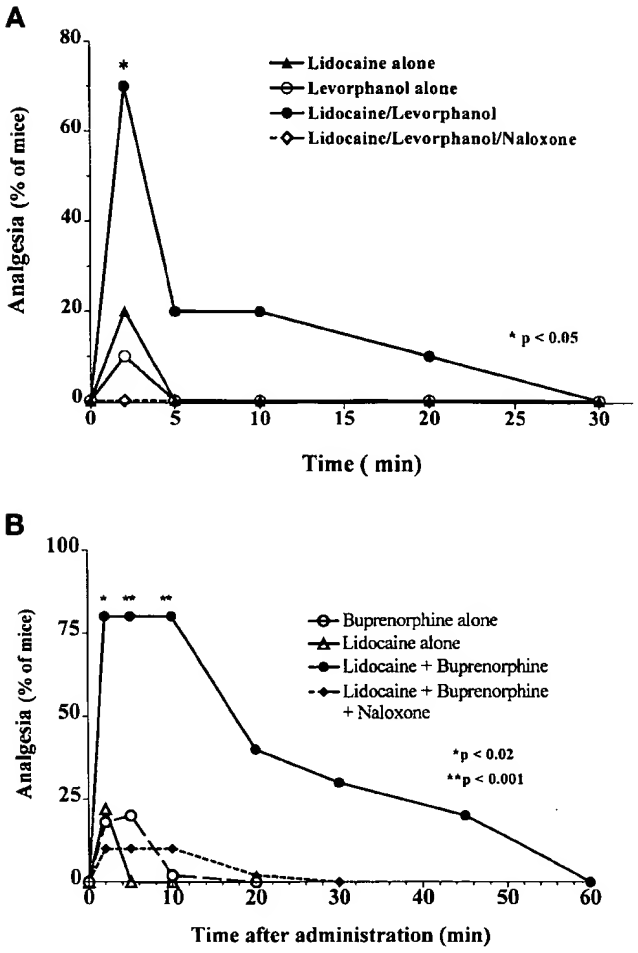

Fig. 5. Effects of combinations of low doses of opioids with lidocaine. A, groups of mice ($n = 20$) received either topical lidocaine (0.9 mM) or levorphanol (1.8 mM) or the combination of the two for 2 min and were tested in the tail-flick assay over 30 min. Another group of mice ($n = 10$) received naloxone (1 mg/kg, s.c.) 20 min before the topical drug application and was tested in tail-flick assay. Naloxone significantly reduced the response. B, groups of mice ($n = 20$) received either topical lidocaine (0.9 mM) or buprenorphine (0.5 mM) or the combination of the two for 2 min and then were tested in the tail-flick assay over 60 min. Another group of animals received naloxone (1 mg/kg, s.c.) 20 min before the topical drug application. Naloxone significantly reduced the response.

current study, lidocaine was effective topically in the radiant heat tail-flick assay, working only on the portion of the tail exposed to the drug and with a potency greater than morphine. As anticipated, the free base was more effective than the salt, presumably due to its greater lipophilicity. However, its dose-response curve was biphasic, with concentrations greater than 20 mM giving a progressive decrease in response. The reasons for this are not clear, but it is interesting that lidocaine concentrations above 15 mM can be toxic to neurons in primary culture (Gold et al., 1998).

All of the opioids tested were effective topical analgesics. The activity of levorphanol and buprenorphine extends the activity to drugs working on opioid systems other than simply mu receptors. Levorphanol elicits analgesia through both mu and $kappa_3$ receptors (Moulin et al., 1988; Tive et al., 1992). Buprenorphine has a complex mechanism of action that is not entirely clear (Leander, 1987; Kamei et al.,

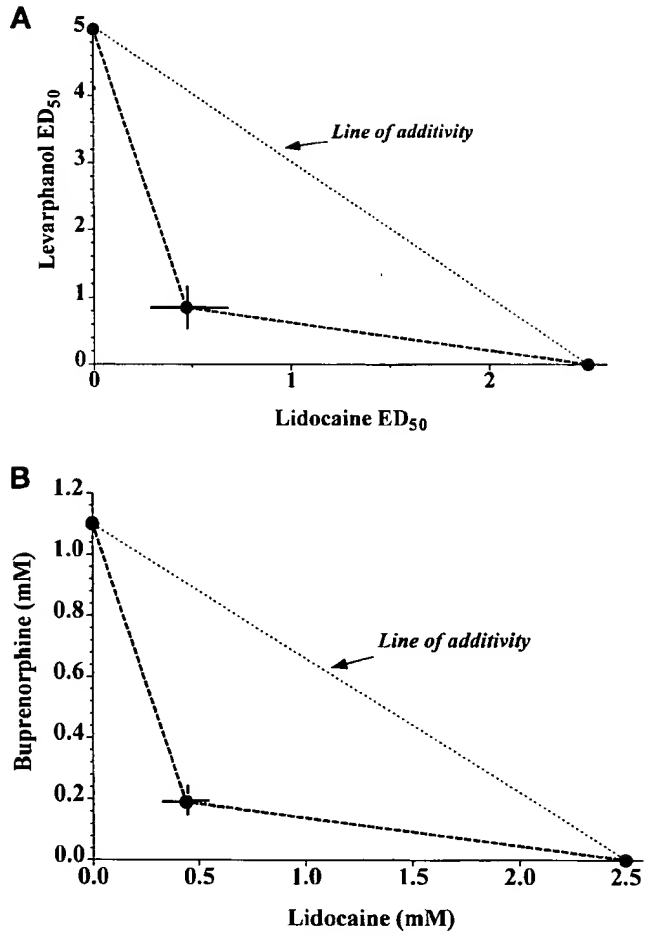

Fig. 6. Isobolographic analysis of lidocaine interactions with levorphanol and buprenorphine. A, using a fixed lidocaine/levorphanol ratio of 0.5, the ED_{50} value of the combination with the 95% confidence limits was determined from the dose-response curve. The point falls below the theoretical line of additivity between the ED_{50} values for each drug alone, indicating synergy. The lack of overlap between the 95% confidence limits for the drugs alone and the combination implies the synergy is significant. B, using a fixed lidocaine/buprenorphine ratio of 2.4, the ED_{50} value of the combination with the 95% confidence limits was determined from the dose-response curve. The point falls below the theoretical line of additivity between the ED_{50} values for each drug alone, indicating synergy. The lack of overlap between the 95% confidence limits for the drugs alone and the combination implies the synergy is significant.

1995a,b, 1997; Walker et al., 1995). Although it has high affinity for virtually all classes of opioid receptors in binding studies, it also has widely varying efficacies for the various classes of receptors. Topically, buprenorphine was particularly effective, with a potency 5-fold greater than that of morphine. The limited ability of naloxone to reverse the combination of buprenorphine and lidocaine implies that at least a portion of the response from buprenorphine was evoked from non-mu-opioid receptors.

Opioid analgesic synergy has been well established. Initially, it was observed among regions simultaneously exposed to opioid (Yeung and Rudy, 1980; Rossi et al., 1993, 1994; Kolesnikov et al., 1996b), followed by the demonstration of synergy between different classes of opioids (Adams et al., 1993). Morphine also has been reported to demonstrate synergy with lidocaine centrally (Saito et al., 1998a,b). We now find synergy peripherally between topical opioids and a local anesthetic.

The combination of a low dose of morphine and lidocaine clearly revealed activity far beyond simple additive interactions, as did similar studies with the other opioids. These strongly suggested synergy among the opioids with lidocaine. This was not unexpected. Synergistic interactions might be more likely when drugs act on different mechanisms, as shown here with the opioids and lidocaine. Isobolographic analysis confirmed synergy between lidocaine and the opioids. The most impressive interaction was between buprenorphine and lidocaine, which had the greatest potentiation and the longest duration of action. However, it is not clear whether this resulted from its receptor selectivity or other factors such as its greater lipophilicity, which would enhance its ability to become diffused through the skin.

The demonstration of synergy between lidocaine and more than one opioid receptor ligand deserves more study. It will be of interest to define the opioid receptor mechanisms involved more clearly. However, even without a full understanding of how these agents interact, the demonstration of topical synergy between a local anesthetic and opioids opens many clinical possibilities in pain management.

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